Biotechnologie Gesellschaft Mittelhessen MBH (BIM)

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New set of claims:

1. A compound having the formula

$$(X - Y_m)_n - S,$$

wherein

X is a pharmaceutically active compound,

Y is a bifunctional linker,

S is a mono-, di- or trisaccharide

n is equal or less than the number of the saccharide units in S, and

m is, independently of n, 0 or 1,

and wherein at least one saccharide unit of S is derived from an aldose monosaccharide comprising a free aldehyde group.

2. The compound of claim 1, wherein m = 0, and X and S are linked to each other by an amide, imine, secondary or tertiary amine, ether, ester, carbonate, carbamate, urea or thioester bond.

3. The compound of claim 1, wherein m = 1, and X and S are linked by means of a pharmaceutical acceptable linking group, said linking group preferably being linked to X and S by an amide, imine, secondary or tertiary amine, ether, ester, carbonate, carbamate, urea or thioester bond and wherein the X-Y bond may be different from the Y-S bond.

4. The compound of any one of claims 1 to 3, wherein S is linear and the saccharide unit(s) within S are linked by α(1-4) bonds.

5. The compound of any one of claims 1 to 4, wherein the viscosity of said compound is 1-100 mPasc, preferably 1-10 mPasc, more preferably 1-7 mPasc.

6. The compound of any one of claims 1 to 4, wherein the molar ratio of X to S is in the range of 20:1 to 1:1, preferably in the range of 15:1 to 1:1, more preferably in the range of 5:1 to 1:1, most preferably about 1:1.

7. The compound of any one of claims 1 to 5, wherein S comprises one or more of the oligosaccharide unit (s) which is (are) identical or different and each selected from the group consisting of:

h) monosaccharides, preferably: ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, fucose;
i) disaccharides, preferably lactose, maltose, isomaltose, cellobiose, gentiobiose, melibiose, primeverose, rutinose;
j) disaccharide homologues, preferably maltotriose, isomaltotriose, lactotriose;
k) uronic acids, preferably glucuronic acid, galacturonic acid;
l) branched oligosaccharides, preferably panose, isopanose,
m) amino monosaccharides, preferably galactosamine, glucosamine, mannosamine, fucosamine, quinovosamine, neuraminic acid, muramic acid; lactosediamine, acosamine, bacillosamine, daunosamine, desosamine, forosamine, garosamine, kanosamine, kansosamine, mycaminose, mycosamine, perosamine, pneumosamine, purpurosamine, rhodosamine;
n) modified saccharides, preferably abequose, amicetose, arcanose, ascarylose, boivinose, chacotriose, chalcose,cladinose, colitose, cymarose, 2-deoxyribose, 2-deoxyglucose, diginose, digitalose, digitoxose, evalose, evernitrose,hamamelose, manninotriose,melibiose, mycarose, mycinose, nigerose, noviose, oleandrose, paratose, rhodinose, rutinose, sarmentose, sedoheptulose, solatriose, sophorose, streptose, turanose, tyvelose.

8. The compound of claim 7, wherein S comprises one or more of the saccharide unit(s) which is (are) selected from the group consisting of glucose, galactose, glucosamine, galactosamine, glucuronic acid, gluconic acid, galacturonic acid, lactose, maltose, maltotriose, isomaltose, isomaltotriose, and neuraminic acid.

9. The compound of any one of claims 1 to 8, wherein the pharmaceutical active compound X is selected from the group consisting of:
antibiotic, anti-diabetic, anti-diuretic, anti-cholinergic, anti-arrhythmic, anti-emetic, anti-epileptic, anti-histaminic, anti-mycotic, anti-sympathotonic, anti-thrombotic, androgenic, anti-androgenic, estrogenic, anti-estrogenic, anti-osteoporotic, anti-cancer, immuno-suppressing, vasodilatory antipyretic, analgesic, anti- inflammatory drugs, blood pressure lowering drugs, antitussiva, antidepressiva, β-blockers, and vitamins.

10. The compound of any one of claims 1 to 9, wherein the pharmaceutically active compound X is selected from the group consisting of:

a) drugs comprising a primary amino group, preferably selected from the group consisting of:
Albuterol, Alendronat, Amikazin, Ampicillin, Amoxicillin, Amphotericin B, Atenolol, Azathioprin, Cefaclor, Cefadroxil, Cefotaxim, Ceftazidim, Ceftriaxon, Cilastatin, Cimetidin, Ciprofloxacin, Clonidin, Colistin, Cosyntropin, Cycloserin, Daunorubicin, Doxorubicin, Desmopressin, Dihydroergotamin, Dobutamin, Dopamin, Ephedrin, Epinephrin, ε-Aminocapronsäure, Ergometrin, Esmolol, Famotidin, Flecainid, Folsäure, Flucytosin, Furosemid, Ganciclovir, Gentamicin, Glucagon, Hydrazalin, Imipenem, Isoproterenol, Ketamin, Liothyronin, Merpatricin, Metaraminol, Methyldopa, Metoclopramid, Metoprolol, Mexiletin, Mitomycin, Neomicin, Netilmicin, Nimodipin, Nystatin, Octreotid, Oxytocin, Pamidronat, Pentamidin, Phentolamin, Phenylephrin, Procainamid, Procain, Propranolol, Ritodrin, Sotalol, Teicoplanin, Terbutalin, Thiamin, Tiludronat, Tolazolin, Trimethoprim, Tromethamin, Vancomycin, Vasopressin, and Vinblastin;

b) drugs comprising a carboxylic acid group, preferably selected from the group consisting of:
Acetylcystein, Azlocillin, Aztreonam, Benzylpenicillin, Camptothecin, Cefamandol, Cefazolin, Cefepim, Cefotaxim, Cefotetan, Cefoxitin, Ceftazidim, Ceftriaxon, Cephalothin, Cilastatin, Ciprofloxacin, Clavulansäure, Dicloxacillin, ε-Aminocapronsäure, Floxacillin, Folinsäure, Furosemid, Fusidinsaure, Imipemem, Indomethacin, Ketorolac, Liothyronin, Melphalan, Methyldopa, Piperacillin, Prostacyclin, Prostaglandine, Teicoplanin, Ticarcillin and Vancomycin.

c) drugs comprising an arylic –OH group, preferably selected from the group consisting of:
Albuterol, Allopurinol, Apomorphin, Ceftriaxon, Dobutamin, Dopamin, Doxycyclin, Edrophonium, Isoproterenol, Liothyronin, Metaraminol, Methyldopa, Minocyclin, Pentazocin, Phenylephrin, Phentolamin, Propofol, Rifamycine, Ritodrin, Teicoplanin, Terbutalin, Tetracyclin and Vancomycin.

d) drugs comprising an aliphatic –OH group, preferably selected from the group consisting of Cyclosporin, Taxol and Paclitaxel.

11. The compound of any one of claims 1 to 10, wherein the bifunctional linker is a linker selected from the group consisting of:

i) linker molecules that connect an –SH group with an amino group, preferably derived from a compound selected from the group consisting of:

AMAS	(N-α(Maleimidoacetoxy)succinimide ester),
BMPS	(N-β(Maleimidopropyloxy)succinimide ester),
GMBS	(N-γ(Maleimidobutyryloxy)succinimide ester),
EMCS	(N-ε(Maleimidocaproyloxy)succinimide ester),
MBS	(m-Maleimidobenzoyl-N-hydroxysuccinimide ester),
SMCC	(Succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate),
SMBP	(Succinimidyl-4-(p-maleimidophenyl) butyrate),
SPDP	(Succinimidyl-3-(2-pyridyldithio) propionate),
Sulfo-GMBS	(N-(γ-Maleimidobutyryloxy)sulfosuccinimide ester), and
Sulfo-EMCS	(N-(ε-Maleimidocaproyloxy)sulfosuccinimide ester);

j) linker molecules that connect two –SH groups, preferably derived from a compound selected from the group consisting of:

BMB	(1.4-Bis-maleimidobutane),
BMDB	(1.4-Bis-maleimido-2.3-dihydroxybutane),
BMH	(Bis-maleimidohexane),

BMOE	(Bis-maleimidoethane),
DTME	(Dithio-bis-maleimidoethane),
HBVS	(1.6-Hexane-bis-vinylsulfone),
$BM(PEO)_3$	(1.8-Bis-maleimidotriethyleneglycol), and
$BM(PEO)_4$	(1.11-Bis-maleimidotetraethyleneglycol);

k) linker molecules that connect two amino groups, preferably derived from a compound selected from the group consisting of:

BSOCOES	(Bis-(2-(succinimidyloxycarbonyloxy)-ethyl)sulfone,
BS^3	(Bis-(sulfosuccinimidyl) suberate DFDNB (1.5-Difluoro-2.4-dinitrobenzene),
DMA	(Dimethyladipimidate 2HCl),
DSG	(Disuccinimidyl glutarate),
DSS	(Disuccinimidyl suberate), and
EGS	(Ethylene glycol bis(succinimidylsuccinate),

l) linker molecules that connect an –SH group and a –CHO functional group, preferably derived from a compound selected from the group consisting of:

BMPH	(N-(β-Maleimidopropionic acid)hydrazide TFA),
EMCH	(N-(ε-Maleimidocaproic acid)hydrazide),
KMUH	(N-(κ-Maleimidoundecanoic acid)hydrazide),
M_2C_2H	(4-(N-Maleimidomethyl)cyclohexane-1-carboxylhydrazide HCl),
MPBH	(4-(4-N-Maleimidophenyl)butyric acid hydrazide HCl), and
PDPH	(3-(2-Pyridyldithio)propionyl hydrazide),

m) linker molecules that connect an –SH group to an –OH group, preferably a compound derived from PMPI (N-(p-Maleimidophenyl)isocyanate);

n) linker molecules that connect an-SH group to a –COOH group, preferably derived from a compound selected from the group consisting of :

BMPA	(N-β-Maleimidopropionic acid),

EMCA (N-ε-Maleimidocaproic acid), and
KMUA (N-κ-Maleimidoundecanoic acid);

o) linker molecules that transform an amino group into a carboxyl group, preferably derived from a compound selected from the group consisting of : MSA (Methyl-N-succinimidyladipate) and its longer and shorter chain homologues or the corresponding ethylene glycol derivatives;

p) linker molecules that transform a –COOH group into an amino group, preferably derived from a compound selected from the group consisting of: DAB (1.4-Diaminobutane) or its longer and shorter chain homologues or the corresponding ethylene glycol derivatives.

12. A process for preparing compounds according to any one of claims 1,2 and 4 to 11, comprising the steps of:

a) coupling one or more pharmaceutically active compound(s) X, comprising an amino, alcohol, and/or thiol group, with one or more aldehyde group(s) of S, or

b) coupling one or more pharmaceutical active compound(s) X, comprising an amino, alcohol, and/or thiol group with one or more carboxylic group(s) of S, or

c) coupling one or more pharmaceutical active compound(s) X, comprising an amino, alcohol, and/or thiol group with one or more activated carboxylic group(s) of S, or

d) coupling one or more pharmaceutical active compound(s) X comprising a carboxyl and/or aldehyde functional group with one or more amino, thiol, or alcohol group(s) of S.

13. The process of claim 12, wherein the coupling in step a) or d) results in the formation of an imine, further comprising the step of reducing the imine to a secondary amine.

14. Process of claim 12 or 13, wherein the imine is reduced by $NaBH_3CN$ at pH values of 6-7.

15. The process of any one of claims 12 to 14, further comprising a step b') or c') prior to step b) or c), respectively, wherein one or more terminal aldehyde group(s) of an S precursor are selectively oxidized to produce the S to be used in step b) or c).

16. The process of claim 15, wherein the one or more terminal aldehyde group(s) of S are selectively oxidized to carboxylic group(s) or activated carboxylic group(s) using

(i) halogen, preferably I_2, Br_2, in alkaline solution, or
(ii) metal ions, preferably Cu^{++} or Ag^{+}, in alkaline solution, or
(iii) electrochemical oxidation.

17. The process of claim 12, wherein in step c) the one or more activated carboxylic group(s) of S are activated carboxylic group(s) selected from the group consisting of a lactone, an anhydride, a mixed anhydride, and a halogenide of a carboxylic acid.

18. The process of claim 12, wherein in step c) the one or more activated carboxylic group(s) of S is (are) a lactone functional group(s).

19. The process of claim 17 or 18, wherein the coupling of a lactone oligosaccharide derivative and one or more pharmaceutically active compound(s) X comprising an amino function is performed in the absence of an activator.

20. The process of claims 18 or 19, wherein the lactone is coupled in non-protic solvents, preferably DMF, DMSO, N-methylpyrrolidone, or alcohols, preferably MeOH, EtOH, n-PrOH, i-PrOH, n-butanol, iso-butanol, tert-butanol, glycol, glycerol.

21. A process for preparing compounds according to claim 1,3 to 11, comprising the steps of:

a) coupling a suitable bifunctional linker group(s) to compound X, and
b) coupling the product(s) of step a) with one or more aldehyde, carboxylic acid, or activated carboxylic group(s) of S, or

a') coupling a suitable bifunctional linker group(s) to one or more aldehyde, carboxylic acid, or activated carboxylic group(s) of S, and

b') coupling the product(s) of step a) with one or more compound(s) X.

22. A process according to claim 21, wherein an imine bond that is formed between the bifunctional linker group and the component X and/or S is further reduced to a secondary amine.

23. Process of claim 22, wherein the imine is reduced by $NaBH_3CN$ at pH values of 6- 7.

24. The process of claim 21, wherein in step b) or step a') the one or more activated carboxylic group(s) of S are activated carboxylic group(s) selected from the group consisting of a lactone, an anhydride, a mixed anhydride, and a halogenide of a carboxylic acid.

25. The process of claims 21 to 24, wherein the bifunctional linker comprises a linear or branched aliphatic chain, preferably an aliphatic chain of 1 to 20, more preferably 1 to 12, most preferably 2 to 6 carbon atoms.

26. The process of claims 21 to 25, wherein the bifunctional linker is a linker selected from the group consisting of:

i) linker molecules that connect an –SH group with an amino group, preferably derived from a compound selected from the group consisting of:

AMAS	(N-α(Maleimidoacetoxy)succinimide ester),
BMPS	(N-β(Maleimidopropyloxy)succinimide ester),
GMBS	(N-γ(Maleimidobutyryloxy)succinimide ester),
EMCS	(N-ε(Maleimidocaproyloxy)succinimide ester),
MBS	(m-Maleimidobenzoyl-N-hydroxysuccinimide ester),
SMCC	(Succinimidyl-4-(N-maleimidomethyl)-cyclohexane-1-carboxylate),
SMPB	(Succinimidyl-4-(p-maleimidophenyl) butyrate),
SPDP	(Succinimidyl-3-(2-pyridyldithio) propionate),
Sulfo-GMBS	(N-(γ-Maleimidobutyryloxy) sulfosuccinimide ester), and
Sulfo-EMCS	(N-(ε-Maleimidocaproyloxy)sulfosuccinimide ester);

j) linker molecules that connect two –SH groups, preferably derived from a compound selected from the group consisting of:

BMB	(1.4-Bis-maleimidobutane),
BMDB	(1.4-Bis-maleimido-2.3-dihydroxybutane),
BMH	(Bis-maleimidohexane),
BMOE	(Bis-maleimidoethane),
DTME	(Dithio-bis-maleimidoethane),
HBVS	(1.6-Hexane-bis-vinylsulfone),
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k) linker molecules that connect two amino groups, preferably derived from a compound selected from the group consisting of:

BSOCOES	(Bis-(2-(succinimidyloxycarbonyloxy)-ethyl) sulfone,
BS_3	(Bis-(sulfosuccinimidyl)suberateDFDNB (1.5-Difluoro-2.4-dinitrobenzene),
DMA	(Dimethyladipimidate 2HCl),
DSG	(Disuccinimidyl glutarate),
DSS	(Disuccinimidyl suberate), and
EGS	(Ethylene glycol bis(succinimidylsuccinate),

l) linker molecules that connect an –SH group and a –CHO functional group, preferably derived from a compound selected from the group consisting of:

BMPH	(N-(β-Maleimidopropionic acid)hydrazideTFA),
EMCH	(N-(ε-Maleimidocaproic acid)hydrazide),
KMUH	(N-(κ-Maleimidoundecanoic acid)hydrazide),
M_2C_2H	(4-(N-Maleimidomethyl)cyclohexane-1-carboxyl-hydrazide HCl),
MPBH	(4-(4-N-Maleimidophenyl)butyric acid hydrazide HCl), and
PDPH	(3-(2-Pyridyidithio)propionyl hydrazide),

m) linker molecules that connect an –SH group to an –OH group, preferably a compound derived from PMPI (N-(p-Maleimidophenyl)isocyanate);

n) linker molecules that connect an –SH group to a –COOH group, preferably derived from a compound selected from the group consisting of:

BMPA	(N-β-Maleimidopropionic acid),
EMCA	(N-ε-Maleimidocaproic acid), and
KMUA	(N-κ-Maleimidoundecanoic acid);

o) linker molecules that transform an amino group into a carboxyl group, preferably derived from a compound selected from the group consisting of: MSA (Methyl-N-succinimidyladipate) and its longer and shorter chain homologues or the corresponding ethylene glycol derivatives;

p) linker molecules that transform a –COOH group into an amino group, preferably derived from a compound selected from the group consisting of: DAB (1.4-Diaminobutane) or its longer and shorter chain homologues or the corresponding ethylene glycol derivatives.

27. A compound according to any of claims 1 to 11 for use as a medicament.

28. A pharmaceutical composition comprising at least one of the compounds according to any one of claims 1 to 11 and a pharmaceutically active carrier.

29. Freeze-dried pharmaceutical composition comprising at least one of the compounds according to any one of claims 1 to 11 and a pharmaceutically active carrier.

30. A kit comprising at least one of the compounds according to any one of claims 1 to 10 in a dehydrated form, preferably in lyophilized form, and at least one physiologically acceptable aqueous solvent.